REMARKS

I. Oath/Declaration

The action again rejected the oath, but per a November 12, 2002 telephone conversation with Examiner Dan Sullivan, the requirement for a new oath is withdrawn.

II. 35 U.S.C. §112, ¶1

Claims 28-51 are rejected under 112(1) as not enabled for treating any disease associated with the liver using any RNA, protein, or polypeptide. The action states on page three that the application is, however, enabled for "a method of treating cirrhosis of the liver by improving the efficiency of in vivo liver cell proliferation by concurrently administering T3 and KGF, the method further comprising administering to the liver cell a retroviral vector complexed with cationic liposomes wherein the retroviral vector encodes HGF, and wherein increased liver cell proliferation leads to amelioration of cirrhosis."

Claim 51 has been amended to add the limitation that the retroviral vector encodes HGF. Based on the above statement from the office action, this claim is now allowable.

To further prosecution, Applicants have also narrowed independent claims 28 and 35 from "diseases associated with the liver" to "diseases directly affecting liver function." A list of many of the diseases that directly affect liver function is found on pages 18 and 19 of the specification. Applicants traverse the remaining 112(1) rejections.

First, the vector in the specification encoded β-galactosidase, which is a reporter gene. The reporter gene merely serves to show that the expression of the gene in the vector is occurring and also allows for measuring the efficiency of transfection. Applicants have

not limited the claims to one or more specific RNA, protein, or polypeptide because the invention shows that any RNA, protein, or polypeptide which can be expressed in liver cells using vectors, can experience enhanced expression with the concurrent administration of T3 and HGF. It would be unrealistic to expect Applicants to test every gene product that could potentially ameliorate a source or condition of a liver-related disease.

It is also very significant to note that the parent case for this application, US Pat. No. 6,248,725, contains claim 11:

> A method for improving the efficiency of in vivo liver cell retroviral transduction, the method comprising, inducing a semi-synchronous wave of in vivo liver cell proliferation by concurrently administering a composition comprising tri-iodothyronine (T3) and keratinocyte growth factor (KGF), **and further comprising administering to the liver a retroviral vector subsequent to the induction of liver cell proliferation, thereby increasing transduction efficiency.** (Emphasis added).

A copy of US Pat. No. 6,248,725 is enclosed with this response. The fact that the parent application issued with a claim containing language that is similar to the rejected language in the present application should be persuasive to allow the claims as presently amended. The issued claim does not list every potential retroviral vector encoding a product that could be administered because it is unnecessary to do so.

The office action also states that the method is enabled for cirrhosis, but no other disease. While this statement is not fully explained, Applicants suppose that only cirrhosis is considered enabled because of the papers of Ueki and Fujimoto discuss cirrhosis and the office action cites these two articles. In reality, the present invention is enabled for cirrhosis

and also for a variety of other diseases that directly affect the liver. Any disease in which proliferation of liver cells and/or expression of a gene product in liver cells is therapeutically effective is contemplated by the present invention. Just because an invention has broad applicability does not mean that Applicants must list every potential disease that could be treated by the invention.

The office action also states (on p. 4-5) that "the specification does not disclose how the increased transduction levels would lead to the treatment and/or prevention of any disease of the liver in a subject." The present invention teaches a method of (1) proliferating liver cells and (2) using those proliferating cells to express a RNA, protein or polypeptide that will treat or prevent a disease directly affecting the liver. The specification lists some potential RNAs, proteins, and polypeptides for therapeutic use on pages 15-17. Obviously, a skilled practitioner would have to assess the liver-related disease and decide what product or products the proliferating liver cells should produce to ameliorate the condition. As both non-final office actions have stated, the level of one of ordinary skill in this art area is very high and the knowledge possessed by one of ordinary skill is likewise sophisticated. This fact weighs in favor of the Applicants.

Again, the office action mentions that there is a nonenabling amount of unpredictability in translating the results of animal systems to humans (p. 6). As explained in detail in section (5) of the June 17, 2002 response to office action, rats are excellent models for translation to human subjects. The office action also restates that there is insufficient guidance provided by the specification for parameters affecting delivery and expression of therapeutic amounts of DNA in the cells (p. 6). Applicants again point out that there are

many locations in which the specification gives specific direction on how to make and use the present invention. In particular, a practitioner may first follow the general procedures set forth at p. 21, lines 1-24 and Example 1, p. 23, lines 11-16 of the specification, to establish a dose response curve for KGF and T3 independently for in vivo liver cell proliferation, and then establish a time course independently for each of the individual factors (specification, Example 2, p. 23, line 16 through p. 24, line 7). After determining the optimal dose and timing for the administration of each of the factors independently, the practitioner administers the factors in such doses and at such times determined to give best results for that species or more specifically, for the individual to determine the effect of co-administering the factors, each at its optimal dose and timing (specification at p. 24, line 8 through p. 25, line 8, Example 3). Significantly, Examples 5 (p. 25, line 20 through p. 26, line 22) and 6 (p. 27, lines 1 though 14) also teach successful transfection and increased expression of a gene product using the present method.

Thus, the specification clearly gives direction regarding administration and dosage of the vector in relation to the stimulatory factors. The specification also gives the exact and specific timing and dosages used in all of the experimental models presented in the Examples (particularly Examples I-VI and the general guidance provided in the specification for timing and dosages, set forth at p. 7, line 16 through p. 10, line 10). Those of skill in the art, having familiarity with translating treatment of rat subjects to treatment of human subjects should be able to discern the appropriate dosages given the individual needs of the patient. Applicants therefore respectfully suggest that the rejection on these grounds also be withdrawn.

Finally, the action again cites the unpredictability of "gene therapy" and the same references against the application. The action then repeats the assertion that gene therapy was not routinely successful at the time of filing (p. 5) and again cites the 1998 Davern reference for the proposition that "gene therapy is a Herculean task." But Applicants have previously cited, Davern then says: "Cautious optimism is warranted. With the objectives now clearly in focus and basic immunology, virology and molecular biology rapidly being applied to this burgeoning technology, we anticipate accelerating progress towards the clinical application of gene therapy for liver disease." (p. 35). Davern obviously sees the future of gene therapy for liver disease and sees that technology advancing at a rapid rate. Applicants suggest that the present invention is an example of that progress.

Applicants note that the "level of predictability in the art" is but one factor in the consideration of enablement and that "all evidence related to each of [the] factors" must be considered and "conclusion of nonenablement must be based on the evidence as a whole." MPEP §2164.01(a). The Office Action is not supported by any 1999 or more recent evidence that would raise a reason to doubt the objective truth of the statements contained in the specification, which must be relied on for enabling support. See MPEP §2164.04. As further evidence of the rapid progress, both Fujimoto (1999) and Ueki (2000) effectively use gene therapy techniques. These papers are proof that gene therapy techniques are generally being widely applied and the impact and possibility for gene therapy extends beyond the specific products produced in those experiments. Applicants assert that this reinforces the argument that the state of the art in gene therapy progresses very quickly and that, in 1999, gene therapy was feasible and not wildly unpredictable.

Additionally, even if some gene therapy failed in 1998, the date of the Davern article, the present invention significantly increases the successful transduction of a given gene in a liver cell because addition of the T3 and KGF. Because none of the other gene therapy methods in the literature discuss these stimulating factors as part of their parameters, it is not accurate to compare those methods to the present method.

Thus, given the present claim amendments and the reasoning presented above, Applicants respectfully request that all 112(1) rejections be withdrawn.

CONCLUSION

In view of the foregoing, it is submitted that the claims are allowable, and issuance of a Notice of Allowance is respectfully requested. Applicants do not believe any fees are associated with this paper, but if necessary, the Commissioner is authorized to charge any fees required by the filing of these papers, and to credit any overpayment to Perkins Coie's Deposit Account No. 50-0665. If Applicants can do anything more to expedite this application, Applicants ask the Examiner to contact the undersigned at (310) 788-9900.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES

IN THE CLAIMS

28. (Twice Amended) A method of treating diseases directly affecting [associated with the] liver function comprising:

inducing a semi-synchronous wave of liver cell proliferation by concurrently contacting the liver cells with tri-iodothyronine (T3) and keratinocyte growth factor (KGF);

contacting the liver cells with a retroviral vector containing a nucleic acid that encodes a RNA, protein or polypeptide to be expressed;

and expressing the RNA, protein or polypeptide.

35. (Twice Amended) A method of treating diseases directly affecting [associated with the] liver function comprising:

the administration of a composition comprising an effective amount of tri-iodothyronine (T3) and an effective amount of keratinocyte growth factor (KGF) , wherein the composition is in an effective amount that induces a semi-synchronous wave of liver cell proliferation upon administration *in vivo* in a subject;

[and] further comprising administering to the liver, subsequent to the liver cell proliferation, a retroviral vector containing a nucleic acid that encodes a RNA, protein or polypeptide to be expressed, wherein expression of the RNA, protein or polypeptide will treat a condition; and

expressing the RNA, protein or polypeptide, thereby treating the condition.

51. (Twice Amended) A method for treating or preventing cirrhosis of the liver comprising concurrently administering to a subject an effective amount of T3 and an effective

amount of KGF, thereby inducing a semi-synchronous wave of liver cell proliferation *in vivo*, and further comprising administering to a liver cell a retroviral vector complexed with cationic liposomes wherein the retroviral vector encodes HGF, which treats or prevents cirrhosis of the liver.

IN THE SPECIFICATION

Please delete the paragraph beginning on page 7, line 18 and ending on page 8, line 9 and replace it with the following paragraph.

The timing, dosage and mode of T3 administration should be determined by the prescribing physician or veterinarian, and may vary depending on the mode of administration, the species, age, and condition of the individual and in accordance with the needs of the individual and the time schedule of administration of other factors. T3 may be administered at any effective time before entrance of liver cells into S-phase is desired. T3 administration may also continue thereafter. Generally, however, T3 may be administered between about 0 and about 28 days before entrance of liver cells into S-phase is desired. Preferably, T3 is administered between about 6 days and about 14 days before entrance of liver cells into S-phase is desired. Most preferably, T3 is administered between about 24 hours and about 8 days before entrance of liver cells into S-phase is desired. More than one administration of T3 may be desirable in accordance with the needs of the individual as determined by the prescribing physician or veterinarian, and T3 may be administered any effective amount of times. Successive administrations generally can be performed at intervals ranging from about hourly to about weekly, but are preferably done at about daily intervals, or by continuous infusion. T3 administration may continue for any effective time after liver cells have begun to proliferate.

Please delete the paragraph beginning on page 10, line 11 and ending on page 10, line 15 and replace it with the following paragraph.

A triple combination of T3, KGF, and hepatocyte growth factor (HGF) was also tried. The cell proliferating characteristics[,] and the transduction efficiency of the triple combination were [was] not statistically significantly different from the T3/KGF combination, although in some experiments the total number of cells induced to proliferate and liver cells transduced may have been slightly higher.